(?penicillin*)
(?dicloxacillin*)

b. *Minor dosage adjustment required* — for drugs which are partially removed by dialysis:

(1) *Hemodialysis*—dosage schedules are relatively well established for patients on chronic twice-weekly dialysis:

tetracycline (oral)	— 0.5 Gm post-dialysis
streptomycin	— 0.5 Gm post-dialysis
gentamicin	— 1 mg/kg post-dialysis
kanamycin	— 7.5 mg/kg post-dialysis
INH	— 300 mg post-dialysis, then 100 mg + pyridoxine q 24 h

(2) *Peritoneal dialysis* — Since long-term regular peritoneal dialysis is rarely used, guidelines for antibiotic dosage are less clearly established. Insufficient amounts of tetracycline are removed to be of significance, and the dosage recommended for the anuric patient should be used. More substantial amounts of kanamycin and streptomycin (and possibly gentamicin) are removed; the dosage suggested for patients on hemodialysis could be used, but the appropriateness of this is uncertain.

c. *Dosage adjustment probably required*—information not adequate:

amphotericin
cephalothin
cephaloridine

It should also be noted that dialysis (peritoneal or hemodialysis) should be used in the management of overdosage with kanamycin and possibly streptomycin and gentamicin, but is unlikely to be of value with other nephrotoxic antibiotic intoxications.

Antibiotics should not be added to the dialysing fluid used in peritoneal dialysis, since they are of no value as prophylaxis against infection and may get absorbed and accumulate in the body.

Table 2 provides an approximate guide to dosage for antibacterial agents in patients with renal insufficiency. Much of the information currently available is inadequate, and *this guide cannot be regarded as definitive.* It should be appreciated that in any individual patient such a dosage guide could result in inadequate or hazardous drug levels unless clinical and laboratory guides are obtained concurrently and appropriate dosage adjustments made as necessary.

*Information inadequate.

ANTIBIOTICS AND LIVER DISEASE

IRVIN JACOBS, M.D.

The following outline is an attempted compilation of known information to serve as a guide in using antibiotic therapy in patients with (a) underlying liver disease and (b) acute liver and gallbladder infections. Unfortunately, precise information is inadequate for many of the drugs. For some drugs very little human data is available for liver tissue antibiotic concentrations, liver histology during treatment, bile levels, and precise metabolic processes in the liver. Indeed, for many older drugs and drugs that are little used, even animal data is scanty.

It is emphasized that often animal data is not applicable to man. A good example is isoniazid, which given long term to dogs produces fatty changes and jaundice; this development is rare in man.

For the most part in treating patients with preexisting liver disease who develop infections outside the liver, one should use caution in prescribing drugs known to be dependent on liver for inactivation or excretion. Usually a safer substitute drug can be found. If a potentially toxic drug must be used, blood levels can be useful in monitoring the dose to within safe limits. One should also take care to avoid use of hepatotoxic non-antibiotic drugs concomitantly.

On the other hand, drugs metabolized and/or excreted by the liver are theoretically ideal for treatment of acute infections of liver and biliary tract.

I. Penicillin G

1. Metabolism by liver: Only minor fraction is ordinarily handled by liver, but in impaired renal function the liver may be a major excretion route via bile.

2. Liver tissue levels: Significant

3. Bile levels: Significant concentration

4. Liver toxicity: Rarely, as part of a generalized hypersensitivity reaction

5. Dose in liver disease:

(a) No change if renal function is good

(b) Reduce dose in circumstance of combined kidney and liver disease.

6. Comment: All penicillins are concentrated in bile even if absolute amount of hepatic excretion is small.

II. Alpha-phenoxy-penicillins

A. Phenoxymethyl

B. Phenoxyethyl (phenethicillin)

C. Phenoxybenzyl (phenbenicillin)

Generally the information for penicillin G applies also for this group. One unique feature of phenbenicillin is that 20% of a dose appears in urine in the form of two metabolities, rather than in unchanged form as with the other penicillins. Site of the metabolic conversion is unknown.

III. Beta Lactamase-Resistant Penicillins

A. Methicillin. Generally the information for penicillin G applies to methicillin.

B. Oxacillin

C. Cloxacillin

D. Nafcillin

Oxacillin and nafcillin have a high percentage excretion into bile. Indeed, with nafcillin, up to 90% of an I.V. dose is accounted for in bile. Oxacillin has induced mild reversible SGOT rises, in one case with a palpable liver.

IV. Broad-Spectrum Penicillins

A. Ampicillin

B. Hetacillin

C. Carbenicillin

Generally the information for penicillin G applies to this group. Ampicillin concentrations in bile may reach as high as 300 times that concurrently present in the plasma; however, the kidneys still account for the major function of the excretion, perhaps 80 percent or more.

In two reports, up to 30 percent of patients on hetacillin 1-2 Gm/day P.O. or I.M. developed laboratory liver function abnormalities without clinical signs; these usually reverted after stopping drug.

I.M. injection of ampicillin in doses of 1 Gm or more can be associated with modest SGOT elevations, which return to normal after stopping drug. The SGOT is possibly released from muscle, rather than liver.

V. Cephalosporins

A. Cephalothin

1. Metabolism by liver: 70-80% usually excreted unchanged in urine. However, it can be inactivated by deacetylation (presumably in liver), then excreted in urine.

2. Liver tissue levels: No information on humans; not concentrated in rats' livers.

3. Bile levels: No good data available.

4. Liver toxicity: Occasional SGOT rise

5. Dose in liver disease: Advisable to decrease in presence of combined renal-hepatic disease.

6. Comment: Many patients develop a positive Coombs' test on drug, but this doesn't correlate with a hemolytic state.

B. Cephaloridine

1. Metabolism by liver: No data; but 70-75% of the drug is accounted for in unchanged form in urine. (There is no acetyl group to split off this compound, as there is with cephalothin.)

2. Liver tissue levels: In rabbits on 200 mg/kg simultaneous levels are:

	LIVER (mcg)	*SERUM (mcg)*
@ ½ hr.	30	100
@ 4 hr.	25	10

In a patient on 1 Gm q4h who died, assay of serum and liver tissue respectively were 58 mcg/ml and 31 mcg/ml.

3. Bile levels: Equal to or below serum.

4. Liver toxicity: Drug may regularly cause modest rise in SGOT, which often reverts while drug is continued. May regularly cause prolonged prothrombin time (up to 29 sec.), though no hemorrhage reported.

5. Dose in liver disease: Same as for cephalothin.

VI. Streptomycin and Dihydrostreptomycin

1. Metabolism by liver: Small fraction is secreted into bile.

2. Liver tissue levels: Appreciable.

3. Bile levels: Not concentrated; up to 10-20 mcg/ml on high doses.

4. Liver toxicity: Rarely reported; also rarely may aggravate existing liver disease.

5. Dose in liver disease: No change.

VII. Tetracyclines

Chlortetracycline, oxytetracycline, tetracycline, demethylchlortetracycline, methacycline, doxycycline

1. Metabolism by liver: All tetracyclines are concentrated in liver and excreted via bile into intestine, where they are reabsorbed. Variable amounts of each member of this drug family are

thereafter eliminated in urine. Chlortetracycline has only 18% eventually eliminated by urine, whereas tetracycline has 60%, oxytetracycline 70%, and methacycline and demethylchlortetracycline 60-70% eliminated eventually in urine. Methacycline and demethylchlortetracycline have prolonged half-lives in the serum because of slower (½) renal clearance than that of tetracycline or oxytetracycline.

2. Liver tissue levels: All are concentrated.

3. Bile levels: 5-32 x the serum level.

4. Liver toxicity: With excess parenteral dose, patients get abnormal LFT's progressing to acidosis, shock, coma and death. Liver lesion is fatty vacuolization with little or no necrosis or biliary stasis. Other organs which may suffer simultaneous toxicity are pancreas, kidneys and brain. Pregnancy and chronic renal disease seem to predispose patients to this type of hepatotoxicity.

5. Dose in liver diseases: Some studies show ½-⅔ of patients with pre-existing hepatic disease get increased fat in liver cells while on tetracyclines. This may revert after stopping drug.

Recommend 1 Gm/day as maximum parenteral dose or use different drug in pregnancy, advanced liver disease, renal disease, or combined hepatic-renal disease. Avoid chlortetracycline completely in liver disease. If dosage adjustment is necessary, avoid exceeding a blood level of 10 mcg/ml.

6. Comments:

(a) By fluorescence and autoradiography, it is demonstrated that liver and kidney concentrate tetracyclines (in mitochondria) more than other organs. Tetracyclines have adverse effects on several hepatic enzymes.

(b) Inactivated chlortetracycline causes same toxic hepatic changes as the active drug; so hepatic toxicity appears not related to antibacterial activity (in mice, dogs).

(c) Tetracyclines may reduce blood coagulation by altering physicochemical characteristics of blood lipoproteins.

(d) Via probable changes in intestinal flora, tetracyclines may decrease plasma prothrombin, and increase urine bilirubin while decreasing urine urobilinogen. This ordinarily causes no clinical problem.

VIII. Chloramphenicol

1. Metabolism by liver: 85-95% is conjugated in liver to monoglucuronide; 3% is further converted to aryl amines and aryl nitro derivatives. Most of above is secreted then by kidney tubules.

2. Liver tissue levels: Concentrated.

3. Bile levels: Average ½ that of plasma.

4. Liver toxicity: Rare.

5. Dose in liver disease: Use caution. If ascites or jaundice is present, use under 25 mg/kg/day or another drug.

6. Comments:

(a) Bone marrow toxicity correlates with high serum levels of free drug; there is no known correlation with levels of metabolic products. It is desirable to keep serum level below 25 mcg/ml of free drug. Though overall chloramphenicol metabolism isn't greatly reduced in hepatic insufficiency, conjugation is slowed and allows more vulnerability to bone marrow toxicity.

(b) Newborns are vulnerable to "grey syndrome" due to immature hepatic and renal function.

IX. Macrolides

A. Erythromycin

1. Metabolism by liver: Major excretory pathway; it is excreted into bile in active form.

2. Liver tissue levels: Concentrated.

3. Bile levels: Concentrated to 5x plasma levels. The estolate form is excreted less in bile than other forms.

4. Liver toxicity: Only by estolate form. Up to 16% of patients after 10-14 days' therapy or repeated courses get elevated transaminase; up to 4% get jaundice with hepatitis symptoms and cholestatic hepatitis on biopsy.

5. Dose in liver disease: Avoid estolate form. Other forms in usual dosage.

6. Comments: Estolate-induced hepatitis is a hypersensitivity reaction. Look for eosinophilia. The syndrome may be reactivated later with a small single oral re-challenge dose of drug.

B. Oleandomycin and triacetyloleandomycin

1. Metabolism by liver: Major.

2. Liver tissue levels: No good data available.

3. Bile levels: Up to 10-15x the peak serum level.

4. Liver toxicity: None from oleandomycin. On triacetyloleandomycin 1 Gm qd x 14 days, up to over 50% of patients may get abnormal liver function tests with or without clinical symptoms. Changes may be dose dependent. Liver biopsies show mixed changes with hepatocellular damage, cholestasis, periportal infiltration and eosinophilia.

5. Dose in liver disease: Avoid.

X. Lincomycin

1. Metabolism by liver: Major; it is excreted and re-excreted via enterohepatic circulation.

2. Liver tissue levels: No data.

3. Bile level: High; can be 10-20x the serum level.

4. Liver toxicity: Occasional jaundice and/or abnormal liver function tests which clear rapidly, sometimes even while drug is continued. No histological information available.

5. Dose in liver disease: Half-life of drug is doubled. Accordingly drug dose should be reduced, or drug avoided entirely.

6. Comment: Relatively new drug, and experience incomplete.

XI. Novobiocin

1. Metabolism by liver: Major.

2. Liver tissue levels: No good data available.

3. Bile levels: 1½-8x serum level.

4. Liver toxicity: uncommonly, liver cell necrosis; occasional patients get biochemical lesion.

5. Dose in liver disease: Unknown, but probably is best to avoid.

6. Comments: This drug may induce "jaundice" by five different methods, all generally uncommon:

(a) Inhibition of glucuronyl transferase in newborns. Up to 7% get high indirect bilirubin and danger of kernicterus without associated liver cell morphological damage.

(b) After 2-14 days' therapy, 0.6% of patients get yellow discoloration of plasma, skin, and sclerae; this is controversially held to be secondary to a circulating lipochrome pigment degradation product of novobiocin.

(c) Occasional adults get increased unconjugated bilirubin and BSP retention with no evidence of morphological disease.

(d) Occasional hemolytic anemia.

(e) Occasional hepatocellular morphological damage with or without cholestasis.

XII. Kanamycin-Neomycin-Paromomycin Group

A. Kanamycin

1. Metabolism by liver: Nil.

2. Liver tissue levels: No data.

3. Bile levels: Up to 10-20x serum levels (but absolute amount is less than 0.5% of total amount of a 1 Gm test dose).

4. Liver toxicity: No.

5. Dose in liver disease:

(a) No change in parenteral dose.

(b) For oral form, see comments.

6. Comments:

In severe liver disease, oral kanamycin at 8 Gm/day eventually builds serum levels to therapeutic range. This effect is even greater with hepatic disease and azotemia. Accordingly, such patients on gut sterilization with kanamycin should be watched for deafness and increasing nephropathy.

B. Neomycin

1. Metabolism by liver: No.

2. Liver tissue levels: No data.

3. Bile levels: No good data available.

4. Liver toxicity: No.

5. Dose in liver disease: No more than 6 Gm P.O. for gut sterilization. If azotemia also present, kanamycin is preferred.

6. Comments: Same apply as for kanamycin. Notably with hepatic disease and azotemia, blood levels on 4 Gm/day P.O. may eventually reach those achieved on parenteral therapy in normals.

C. Paromomycin

This drug is only used orally for gut sterilization, and is only minimally absorbed. There is no liver toxicity. Probably kanamycin is preferred for gut sterilization in hepatic coma with azotemia.

XIII. Polymyxin - Colistin Group

1. Metabolism by liver: Minor, if any.

2. Liver tissue levels: No good data available.

3. Bile levels: Low.

4. Liver toxicity: No.

5. Dose in liver disease: No change.

XIV. Vancomycin

This drug is minimally, if at all, metabolized by liver. Very little is present in bile. No liver toxicity is reported.

XV. Nitrofurantoin

1. Metabolism by liver: 50-60% is metabolized at unknown site.

2. Liver tissue levels: No good data available.

3. Bile levels: No good data available.

4. Liver toxicity: Rarely, causes a hypersensitivity hepatitis with cholestasis, focal necrosis, infiltrates, eosinophils.

5. Dose in liver disease: Probably no change.

6. Comment: May cause hemolytic anemia with jaundice in G6PD deficient patients.

XVI. Sulfonamides

1. Metabolism by liver: Metabolism is significantly, but not solely by liver (acetylation, glucuronidation, and/or oxidation), then excreted into urine.

2. Liver tissue levels: Significant.

3. Bile levels: Similar to plasma.

4. Liver toxicity: Two types, not influenced by dose: direct hepatotoxicity and hypersensitivity. Either may go on to acute yellow atrophy.

5. Dose in liver disease: Best to avoid sulfas.

(a) Pre-existing nutritional liver disease may predispose to sulfonamide hepatotoxicity.

(b) Kidneys appear to be more susceptible to damage by sulfas in patients with chronic liver disease.

(c) Neonates have reduced acetylation, thus require less dose for therapeutic blood levels.

6. Comments:

(a) Incidence of reported hepatic injury secondary to sulfonamides is greatly decreased (to 0.1%) since the introduction of sulfadiazine and subsequent other new compounds.

(b) Acetylated and glucuronide forms circulating in blood prior to renal excretion contribute to toxicity but not to antibacterial effect.

(c) Sulfas may induce hemolytic anemias in G6PD deficient patients.

(d) Long-acting forms are particularly dangerous in the event of a toxic reaction since drug levels persist long after the drug is discontinued.

XVII. Amphotericin B

1. Metabolism by liver: Minor.

2. Liver tissue levels: No good data available.

3. Bile levels: No good data available.

4. Liver toxicity: May be rarely idiosyncratic, or due to excess dose (i.e., greater than 1 mg/kg/dose). The picture is acute failure with toxic degeneration, fatty liver and cholestasis.

5. Dose in liver disease: Unknown, but caution advised.

XVIII. Antituberculosis Drugs

A. Streptomycin: See above.

B. Isoniazid.

1. Metabolism by liver: 40-90% is excreted by kidneys; but a significant variable amount is inactivated by acetylation and other changes via liver enzyme(s), then excreted in urine.

2. Liver tissue levels: High.

3. Bile levels: Data in rabbits suggest 1½x the average serum level.

4. Liver toxicity: Rarely on therapeutic doses, patients may get either toxic or hypersensitivity hepatitis.

5. Dose in liver disease: Probably no change.

6. Comments: About 50% of patients are "slow inactivators," an autosomal homozygous recessive trait, i.e., they acetylate INH slowly, thereby having prolonged active drug levels. Slow inactivators should take pyridoxine daily.

Some workers feel "rapid inactivators" should get maximum doses for T.B. meningitis, but standard doses for pulmonary T.B. are adequate.

Note: Pyridoxine is a coenzyme of transaminases, and given daily may cause spuriously elevated transaminase activity.

C. Para-aminosalicylic acid

1. Metabolism by liver: 50-65% is acetylated (possibly by a liver enzyme), then excreted into urine.

2. Liver tissue levels: High.

3. Bile levels: No good data available.

4. Liver toxicity:

(a) Generalized hypersensitivity reactions (2-5%) may progress to include liver cell

necrosis (uncommon), and/or cholestasis; it may be fatal.

(b) May suppress prothrombin formation in liver; usually not a clinical problem.

5. Dose in liver disease: No good data available.

6. Comments:

(a) Continued use of drug in presence of early hypersensitivity reactions can lead to progression to more serious symptoms. Accordingly, drug should be discontinued. Some workers feel desensitization can be done successfully.

(b) Occasional hemolytic anemia occurs.

(c) Apparently competes with INH for acetylation, thereby increasing free INH levels.

D. Ethionamide

1. Metabolism by liver: Unknown, but less than 1% is excreted in urine in active form.

2. Liver tissue levels: Same as blood presumably.

3. Bile levels: Data in rabbits suggest 1½x average serum level.

4. Liver toxicity: Occasional toxic or hypersensitivity hepatitis, usually in diabetics.

5. Dose in liver disease: Unknown; close monitoring of renal and hepatic function advised.

E. Pyrazinamide

1. Metabolism by liver: Minor.

2. Liver tissue levels: No good data available.

3. Bile levels: No good data available.

4. Liver toxicity: Toxic hepatitis in 10-20% of patients is dose dependent and usually occurs late (2nd-6th month). It may be fatal.

5. Dose in liver disease: Avoid.

6. Need for careful monitoring of liver functions limits its usefulness.

F. Cycloserine

1. Metabolism by liver: 35% is metabolized at unknown site(s).

2. Liver tissue levels: No good data available.

3. Bile levels: Present, but none reaches stool.

4. Liver toxicity: Not reported.

G. Ethambutol

1. Metabolism by liver: 70-95% is excreted in urine of which 8-15% appears as metabolites. Site of the conversions is unknown.

2. Liver tissue levels: No good data available.

3. Bile levels: Unknown.

4. Liver toxicity: Mild SGOT rise noted in some patients on 25 mg/kg for several months.

5. Dose in liver disease: No change.

6. Comment: New dose recommendation is 15 mg/kg/day in patients on drug over 60 days. This gives adequate therapeutic effect, and avoids ocular toxicity and SGOT elevations.

H. Viomycin

Metabolism by liver is minimal. Very little is known of its metabolism except it is mainly excreted in urine. No liver toxicity reported.